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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/067,705	SAWYERS ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 21-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 21-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/2/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Response and Amendment, filed 7/18/05, has been entered and considered. Claim 22 has been amended; claims 1, 21-25 are pending and under current examination.

Double Patenting

The terminal disclaimers, filed 7/18/05, over U.S. Pat. No. 6,365,797 B1, 6,107,540, 6,828,471 and 6,815,574 are proper and have been entered.

Claims 1 and 21-25 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over allowed claims 21-27 of copending Application No. 10/062,738, which is now allowed. This rejection is maintained for reasons of record. This rejection is maintained because no Terminal Disclaimer of record has been filed.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Information Disclosure Statement

Applicants' IDS, filed 8/2/05, has been considered and made of record.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 24 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Stearns and Wang (1992, Cancer Research 52: 3778-3781, cited as document C3 on Applicants' IDS, filed 8/2/05).

The claims are directed to an immune deficient SCID mouse model having a human prostate cancer xenograft of locally advanced or metastatic prostate cancer; wherein the mouse recapitulates the development of primary tumors, micrometastasis, or formation of osteoblastic lesions characteristic of late stage prostate cancer. In specific embodiments, the xenograft is an explant from prostate, lymph node, lung, or bone tissue.

Stearns and Wang teach that PC-3 ML human prostatic tumor cells were injected i.v. into the tail vein of SCID mice (Stearns and Wang, page 3779, 2nd col., parag. under "Effect of Taxol on tumor Growth *in Vivo*"). On the 6th day following tumor inoculation, the mice were injected i.v. via the tail vein with taxol (50 mg/m^2/day and 250 mg/m^2/day in 0.2 ml). Ten mice were treated with each taxol dosage tested and five control mice received equivalent amounts of polyoxyethylated castor oil, the vehicle in which taxol was formulated. 15 days after treatment, the mice were sacrificed and examined for tumors by dissection and histology. Gross dissection revealed that tumors grew specifically in the lumbar vertebrae (i.e. filling the bone marrow) in all the control mice. Gross dissection of the taxol treated mice showed that none of the 20 mice exhibited noticeable tumors in any tissues examined (lungs, liver, colon, testicles, muscle, brain, vertebrae). 20 days after treatment, there was tumor tissue, but only in the bone marrow of the lumbar vertebrae of the taxol treated mice. The tumor burden in mice exposed to 50 mg/m^2/day or 250 mg/m^2/day taxol was minimal and about the same as that observed in untreated mice sacrificed at day 5 (Stearns and Wang, page 377, 2nd col., parag. under "Effect of Taxol on tumor Growth *in Vivo*" to page 3780, 1st col., 1st parag.).

Therefore, Stearns and Wang anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 21, 24 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stearns & Wang (cited above) when taken with Crowley *et al.*, (1993, PNAS, USA, 90: 5021-5025, document C2 of Applicants' IDS, filed 8/2/05).

Stearns and Wang teach that PC-3 ML human prostatic tumor cells were injected i.v. into the tail vein of SCID mice (Stearns and Wang, page 3779, 2nd col., parag. under "Effect of Taxol on tumor Growth *in Vivo*"). On the 6th day following tumor inoculation, the mice were injected i.v. via the tail vein with taxol (50 mg/m^2/day and 250 mg/m^2/day in 0.2 ml). Ten mice were treated with each taxol dosage tested and five control mice received equivalent amounts of polyoxyethylated castor oil, the vehicle in which taxol was formulated. 15 days after treatment, the

mice were sacrificed and examined for tumors by dissection and histology. Gross dissection revealed that tumors grew specifically in the lumbar vertebrae (i.e. filling the bone marrow) in all the control mice. Gross dissection of the taxol treated mice showed that none of the 20 mice exhibited noticeable tumors in any tissues examined (lungs, liver, colon, testicles, muscle, brain, vertebrae). 20 days after treatment, there was tumor tissue, but only in the bone marrow of the lumbar vertebrae of the taxol treated mice. The tumor burden in mice exposed to 50 mg/m^2/day or 250 mg/m^2/day taxol was minimal and about the same as that observed in untreated mice sacrificed at day 5 (Stearns and Wang, page 377, 2nd col., parag. under "Effect of Taxol on tumor Growth *in Vivo*" to page 3780, 1st col., 1st parag.).

Sterans and Wang do not teach the implantation of the xenograft subcutaneously. However, prior to the time of the claimed invention, Crowley *et al.* teach that human PC3 prostate carcinoma cells were inoculated subcutaneously into nude mice. These cells were transfected with a reporter construct comprising a CAT reporter. Eight weeks after subcutaneous inoculation of these cells into nude mice, CAT activity was used to detect the cells in regional lymph nodes, femurs, lungs, and brain, and thus mimicked the organ tropism observed for naturally occurring metastases of prostate cancer (Crowley et al., page 5022, 2nd col. 1st parag. under Results, see also Table 1). Crowley et al. also teach that PC3 cells were transfected with the CAT reporter construct and a construct comprising a nucleic acid sequence encoding a mutant u-PA (Ser^{356} to Ala) which lacks enzymatic activity but which retains full receptor binding affinity. While tumor growth in the cells comprising mutant uPA construct was similar to that of cells not comprising the construct, Crowley et al. teach that mice injected with cells comprising the mutant uPA construct exhibited background levels of lymph node CAT activity, indicating that these clones were unable to establish metastatic tumor foci within the regional lymph nodes. In addition to this, the levels of CAT activity in cells

comprising mutant uPA were 40 to 100 fold lower in the brain and 10 to 20 fold lower in lungs (Crowley et al., page 5023, 2nd col., 2nd parag.).

Accordingly, in view of the combined teachings, it would have been obvious to make a mouse model, by using a SCID mouse and subcutaneously implanting a human prostate cancer xenograft of locally advanced or metastatic prostate cancer to produce the claimed mouse model, with a reasonable expectation of success. One of skill in the art would have been sufficiently motivated to make such a modification, as Crowley supports that producing their mouse model allows the metastasis of human tumor cells, which could then be used to test the efficacy of potential therapeutic agents *in vivo*. See p. 5025, col. 1-2, bridging ¶.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 1, 22, 24, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stearns & Wang (cited above) when taken with Monosov et al. (U.S. Patent 5,491,284, patented, February 13, 1996; filed December 17, 1993, document C1 of Applicants' IDS, filed 8/2/05).

Stearns & Wang are summarized above. They do not teach transplantation of the xenograft intraprostatically. However, prior to the time of the claimed invention, Monosov *et al.* teach how to make a mouse model for cancer. Monosov *et al.* teach that the embodiments that are used to make the mouse model encompass that the human neoplastic tissue is intact and is transplanted onto the corresponding organ of the non-human mammalian model, wherein the model is sufficiently immunodeficient to allow the transplanted tissue to grow and mimic the progression of neoplastic disease in the human donor (col. 3, 1st parag.). Monosov *et al.* teach that implantation of tissue from a human prostatic carcinoma into the prostate of a recipient animal is carried out by surgically forming an opening in the prostate and then placing 5 tissue specimens of approximately 0.1x0.1x0.1 cm in

size under the prostate capsule. After placement of the tissue specimen, the opening in the capsule is closed with appropriate sutures (col. 5, 3rd parag.). Monosov *et al.* teach that the animal model can be used to screen new anti-neoplastic agents to determine the ability of such agents to affect tumors at the primary site and also at distant metastatic sites or to prevent distant metastases from occurring. The models are also useful for individualized chemosensitivity testing of a cancer patient's tumors (col. 7, 4th parag.)

Accordingly, in view of the combined teachings, it would have been obvious to make a mouse model, by using a SCID mouse and intraprostatically implanting a human prostate cancer xenograft of locally advanced or metastatic prostate cancer to produce the claimed mouse model, with a reasonable expectation of success. One of skill in the art would have been sufficiently motivated to make such a modification, as Monosov supports that there is an art-recognized need for a representative animal for human neoplastic disease, and that this animal model would be used in drug screening, testing and evaluation. See col. 1, lines 21-32.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

Claim 23 is free of the prior art of record, wherein the xenograft is implanted within the bone of a mouse. Claim 23 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claims and any intervening claims. Claim 23 depends on claim 1, which is anticipated by the art.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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